UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/461,090	12/14/1999	AXEL ULLRICH	P564-9051	3321

7590 05/21/2002

ARENT FOX KINTNER PLOTKIN & KAHN, PLLC
1050 CONNECTICUT AVENUE
SUITE 600
WASHINGTON, DC 20036-5339

EXAMINER
LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/21/2002

21

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/461,090	ULLRICH ET AL.	
	Examiner	Art Unit	
	Frank Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 8-21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5 and 8-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 16, 2002 has been entered as Paper No: 12. The claims pending in this application are claims 1, 3-5, and 8-21.

Drawings

2. Applicant's request "one any claims have been allowed, Applicants will submit formal drawings" has been granted by the examiner.

Claim Objections

3. Claim 17 is objected to because of the following informalities: "the growth receptor activation" should be "the growth-factor receptor activation".

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

> person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1, 17-19, and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method for treating a subject with a disorders associated with a disturbed growth factor receptor activation by G-protein mediated signal transduction using a method for modulating growth-factor activation by G-protein-mediated signal transduction comprising contacting the extracellular domain of a cell or an organism containing a growth-factor receptor capable of activation by G-protein mediated signal transduction with a compound effecting a protinase or a ligand precursor for the growth-factor receptor. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry

and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001) (see below).

The Breadth of The Claims

The claims 1, 17-19, and 21 encompass a method for treating any kind of subject with any kind of disorder associated with a disturbed any kind of growth factor receptor activation by any kind of G-protein mediated signal transduction using a method for modulating growth-factor activation by G-protein-mediated signal transduction comprising contacting the extracellular domain of any kind of cell or any kind of organism containing any kind of growth-factor receptor capable of activation by any kind of G-protein mediated signal transduction with a compound effecting any kind of protinase or the ligand precursor for any kind of growth-factor receptor.

Working Examples

The specification provides working examples (see pages 6-17) to show that inhibition of proHB-EGF processing by a metalloproteinase inhibitor, batimastat, blocks EGF receptor transactivation by G-protein-coupled receptors in *in vitro*.

The Amount of Direction or Guidance Provided and The State of The Prior Art

There is no direction or guidance in the specification to show how to treat a subject with a disorder associated with a disturbed growth factor receptor activation by G-protein mediated signal transduction such as cancer or asthma as recitedin claims 17-19 and 21. It is unclear how

a method for modulating growth-factor activation by G-protein-mediated signal transduction comprising contacting the extracellular domain of any kind of cell or any kind of organism containing any kind of growth-factor receptor capable of activation by any kind of G-protein mediated signal transduction with a compound effecting any kind of protinase or the ligand precursor for any kind growth-factor receptor as recited in claim 1 can be used to treat any disorder associated with a disturbed growth factor receptor activation by G-protein mediated signal transduction since the method recited in claim 1 is not directed to a method for treating a disorder. Although it was known that a metalloproteinase inhibitor, KB-R7785 could attenuate pressure overload cardiac hypertrophy and cardiac hypertrophy induced by phenylephrine (PE) or angiotensin II (Ang II) in mice (see Asakura et al., Nature Medicine, 8, 35-40, January 2002 and Liao, Nature Medicine, 8, 20 and 21, January 2002), during the process of the prior art search, the examiner did not find prior art which related to treat any kind of subject with any kind of disorder associated with a disturbed growth factor receptor activation by G-protein mediated signal transduction using a method recited in claim 1.

Level of Skill in The Art, The Unpredictability of The Art, and The Quantity of Experimentation Necessary

While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether a method for modulating growth-factor activation by G-protein-mediated signal transduction comprising contacting the extracellular domain of a cell or an organism containing a growth-factor receptor capable of activation by G-protein

mediated signal transduction with a compound effecting any kind of protinase or a ligand precursor for the growth-factor receptor as recited in claim 1 can be used in treating any kind of subject with any kind of disorder associated with a disturbed growth factor receptor activation by G-protein mediated signal transduction. It has been well known in the art that research *in vitro* could provide a direction for in *vivo* study and a method for using a drug that worked in *in vitro* for treating certain disease such as a cancer, in the most time, does not work or does not work efficiently in human body due to various different reasons (see Science, 278, 1041 and 1042, 1997). Since the specification does not provide any guidance for *in vivo* treatment, there will be a lot of unpredictable factors when the skilled artisan uses the method recited in claim 1 to treat disorders associated with growth factor receptor such as the treatment of cancer or asthma and the skilled artisan will have no way to predict the experimental results. With the predictability in the relevant art being low, the amount of experimentation needed to be exerted by the public in practicing the full scope of the invention would not fall within the limits of routine experimentation. Such efforts constitute undue experimentation. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001 (see above). As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v.*

> *Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed.

Response to Arguments

In page 6, fifth paragraph of applicant's remarks, applicant argued that " a recent publication by Asakura et al. (Nature Medicine 8 (2002), 35-40) and the accompanying article by Liao." can considered "[A]s proof of the in vivo applicability of the method according to the invention for the treatment of heart diseases,".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection. Although Asakura *et al.,* showed that a metalloproteinase inhibitor, KB-R7785 could attenuate pressure overload cardiac hypertrophy and cardiac hypertrophy induced by

phenylephrine (PE) or angiotensin II (Ang II) in mice, the method taught by Asakura *et al.*, was totally different from claimed invention because: (1) claimed invention does not limit to mice with cardic hypertroph but is directed to a method for treating any kind of subject with any kind of disorder associated with a disturbed growth factor receptor activation by G-protein mediated signal transduction using specific metalloproteinase inhibitor, KB-R7785; and (2) the specification does not disclose the method taught by Asakura *et al.*, and there is no description in the specification related to treating cardiac hypertrophy using KB-R7785. In fact, the specification does not provide any guidance for *in vivo* treatment.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 3-5, and 8-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Note that claims 3-5, 8-19, and 21 are dependent on claim 1.

8. Claims 1, 16, and 20 are rejected as vague and indefinite becuase it is unclear what it intended. For example, how a compound effecting any kind of proteinase or a ligand precursor for the growth-factor receptor can modulating growth-factor receptor activation since not every proteinase was related to growth-factor receptor activation? How a compound that can modify but does not affect release of a ligand precursor the growth-factor receptor can modulate growth-factor receptor activation by G-protein protein-mediated signal transduction? Please clarify.

9. Claim 1 rejected as vague and indefinite because preamble of the claim does not correspond to the method step in the claim (the goal of the method recited in claim 1 does not reach).

10. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how to treating a subject with a disorder associated with or accompanied by a disturbed growth factor receptor activation by G-protein mediated signal transduction (no treatment steps).

Claim Rejections - 35 USC § 102/103

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 3-5, 8-10, 12-15, and 20 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Dong *et al.,* (Proc. Natl. Acad. Sci. USA, 96, 6235-6240, May 1999).

Regrading claims 1, 4, 5, 8-10, 12, 13, 15, and 20, Dong *et al.,* teach metalloprotease-mediated ligand release regulates autocrine signaling through the epidermal growth factor receptor. As acknowledged by Dong *et al.,* ligands that activated the epidermal growth factor receptor (EGFR) were synthesized as membrane-anchored precursors as recited in claim 10 that appeared to be proteolytically released by members of the ADAM family of metalloproteases as recited in claims 9 and 12. This membrane-anchored EGFR ligands were thought to be biologically. In this study, they used metalloprotease inhibitors as recited in claims 8 and 13 to block EGFR ligand release from human mammary epithelial cells. These cells expressed both transforming growth factor α and amphiregulin and required autocrine signaling through the EGFR (extracellular domain) for proliferation and migration. They found that a metalloprotease inhibitor, batimastat as recited in claim 15 (see page 6236, Figure 1), reduced cell proliferation in direct proportion to their effect on transforming growth factor α release. This metalloprotease inhibitor also reduced growth of EGF-responsive tumorigenic cell lines and were

synergistic with the inhibitory effects of antagonistic EGFR antibodies. Blocking release of EGFR ligands also strongly inhibited autocrine activation of the EGFR and reduced both the rate and persistence of cell migration. The effects of this metalloprotease inhibitor could be reversed by either adding exogenous EGF or by expressing an artificial gene for EGF that lacked a membrane-anchoring domain (page 6235, abstract). The effect of batimastat on the activation of tyrosine phosphorylation as recited in claim 4 was also be examined (see page 6238, right column and Figure 4). Note that: (1) the phrase " a method for modulating growth receptor activation by G-protein-mediated signal transduction" in claim 1 and " a method for identifying compound for modulating growth receptor activation by G-protein-mediated signal transduction" in claim 20 were preambles and was not considered as the limitations in this rejection. Note that a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951); (2) "capable of activation by G-protein mediated signal transduction by its extracellular domain" in claim 1 and "capable of activation by G-protein mediated signal transduction" in claim 20 could be considered as inherent properties of EGF receptor since EGF receptor taught by Dong *et al.*, has this property.

Regrading claim 3, EGF ligands such as transforming growth factor α activated to EGF receptors by binding to their extracellular domain.

Regrading claim 14, although Dong *et al.,* did not directly show metalloproteases they used was a zinc-dependent proteinase, in the absence of convincing evidence to the contrary, this limitation was considered to be inherent to the reference taught by Dong *et al.,* since it has been known that the ADAM family of metalloproteases are zinc-dependent proteinases (see Rosendahl *et al.,* J. Biol. Chem., 272, 24588-24593, 1997 and Kaushl *et al.,* J. Clinical Investigation, 105, 1335-1337, 2000).

Response to Arguments

In page 8, fourth and fifth paragraphs of applicant's remarks, applicant argued that "the claims do not read on, and therefore are not anticipated by Dong" since "[D]ong is specifically silent that the instantly claimed therapeutic approach can be applied in the modulation of disorders associated with the G-protein of the GPCR".

This argument has been fully considered but it is not persuasive toward the withdrawal of the rejection because the examiner did not reject the claims related to therapy (see claims 17-19 and 21).

14. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dong *et al.,* (May 1999) as applied to claims 1, 3-5, 8-10, 12-15, and 20 above, and further in view of Miyoshi *et al.,* (J. Biol. Chem., 272, 14349-14355, 1997).

The teachings of Dong *et al.*, have been summarized previously, *supra.*

Dong *et al.*, do not disclose to use a cell line that can produce pro-HB-EGF as recited in claim 11 in the assay.

Miyoshi *et al.,* do teach to use a cell line that can produce pro-HB-EGF such as AH66tc (see abstract in page 14349 and pages 14349, 14351, and 14352).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 1 using a cell line that can produce pro-HB-EGF in view of the references of Dong *et al.,* and Miyoshi *et al.,* so that HB-EGF released from pro-HB-EGF can activate EGF receptors by binding to their extracellular domain. One having ordinary skill in the art would have been motivated to modify the method of Dong *et al.,* because the simple replacement of one cell line with well known properties (a human mammary epithelial cell line) from another cell line with well known properties (cell line that can produce pro-HB-EGF) would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Conclusion

15. No Claim is allowed.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
May 14, 2002